



0 445 467 A1

EUROPEAN PATENT APPLICATION

- (21) Application number: 90313104.3
(22) Date of filing: 03.12.90

- ⑤ Int. Cl.⁵: C07K 5/02, C07K 5/06,
A61K 37/64

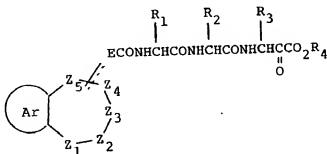
The title of the invention has been amended (Guidelines for Examination in the EPO, A-III, 7.3).

- (20) Priority: 08.12.89 GB 8927872
- (42) Date of publication of application:
11.09.91 Bulletin 91/37
- (46) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE
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- (c) Compounds of formula (I), and pharmaceutically acceptable salts thereof:



(I)

having renin inhibitor activity, a process for their preparation and their use as pharmaceuticals.

PHARMACEUTICALS

The invention relates to novel compounds having pharmacological activity, to processes for their preparation, to pharmaceutical preparations containing them and to their use in medicine.

operation, to pharmaceutical preparations containing them and to their use.

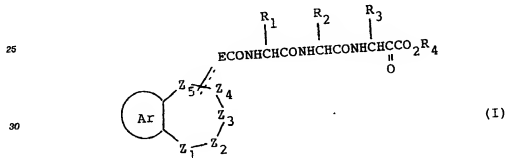
Renin is a natural enzyme, disorders in relation to which are implicated in many cases of hypertension. It is released into the blood from the kidney, and cleaves from a blood glycoprotein a decapeptide known as angiotensin-I. Circulating angiotensin-I is cleaved in plasma, and in lung, kidney and other tissues to an octapeptide, angiotensin-II, which raises blood pressure both directly by causing arteriolar constriction and indirectly by stimulating release of the sodium-retaining hormone aldosterone from the adrenal gland and thus causing a rise in extracellular fluid volume. The latter effect is caused by angiotensin-II itself or a heptapeptide cleavage product angiotensin-III.

Angiotensin is useful in the treatment of hypertension.

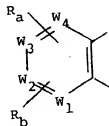
10 inhibitors of renin have been described as useful in the treatment of hypertension. These include the naturally occurring heptapeptide cleavage product angiotensin-III, which has been discovered, which inhibit the enzyme renin.

Inhibitors of renin have been described as useful in the treatment of hypertension. A group of compounds has now been discovered, which inhibit the enzyme renin and therefore have potential blood pressure lowering activity, useful in the treatment of hypertension. Compounds having an associated mechanism of action have also been described as possessing anti-retroviral activity and the present compounds may therefore be of potential use in the treatment of diseases caused by retroviruses including human immunodeficiency virus (HIV-1 and 2) and HTLV I and II. They may also be of potential use in the treatment of other cardiovascular disorders, such as congestive heart failure, and have beneficial effects on learning and memory and mood elevation activity, of potential use in the treatment of CNS disorders such as Alzheimer's disease and depression; they may also be of potential use in the treatment of glaucoma.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



35 wherein
the Ar ring is of sub-formula (a) or (b):



(a)



(b)

one or two of W_1 , W_2 , W_3 and W_4 is CH, N or NO (such that if two are NO then these are W_1 and W_4), and the others are CH, CR_a or CR_b ;

one of Q_1 , Q_2 and Q_3 is S and the other two are CH and CR_c ;

either Z_1 and Z_2 are absent and Z_3 , Z_4 and Z_5 and the carbon atoms to which Z_3 and Z_5 are attached, form a 5-membered non-aromatic heterocyclic ring; or

Z_1 is absent and Z_2 , Z_3 , Z_4 , Z_5 and the carbon atoms to which Z_2 and Z_5 are attached, form a 6-membered non-aromatic heterocyclic ring; or

Z_1 , Z_2 , Z_3 , Z_4 and Z_5 and the carbon atoms to which Z_1 and Z_3 are attached, form a 7-membered non-aromatic heterocyclic ring;

E is absent or is $(CH_2)_n$ or $CH(CH_2)_{n-1}$ wherein n is 1 to 4;

R_a and R_b are independently selected from hydrogen or a substituent;

R_1 is CH_2R_9 wherein R_9 is optionally substituted aryl or heteroaryl;

R_2 is $CH(R_{10})R_{11}$, wherein R_{10} is hydrogen or methyl and R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted aryl or heteroaryl, or R_{11} is amino, C_{2-7} alkanoylamino, 2-oxopyrrolidinyl, 2-oxopiperidinyl or C_{1-6} alkoxycarbonylamino;

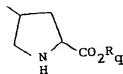
R_3 is CH_2R_{12} wherein R_{12} is C_{1-6} alkyl or C_{3-8} cycloalkyl or phenyl;

R_4 is C_{1-6} alkyl, C_{2-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-4} alkyl or a group of structure c), d), e) or f);

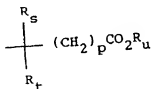
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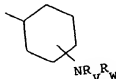
d)



e)

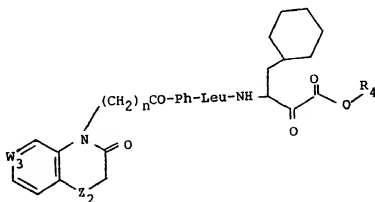


f)



wherein

R_p , R_q , R_r , R_s , R_t , R_u , R_v and R_w are selected from hydrogen or C_{1-6} alkyl; or NR_vR_w is 1-imidazolyl; and

Compound/Ex. No.W₃Z₂nR₄

Ex. 2

BOC-NHCH₂-C

O

2

iPr

Ex. 3

H₂NCH₂-C

O

2

iPr

Ex. 4

N

S

2

iPr

Ex. 5

N

S

3

iPr

Ex. 6

N

S

2

*

*4- (1-methylpiperidinyl)

Example 2

40
Isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate

45
This material was formed from isopropyl 2-(1-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 5(1)) (0.21g) following the procedure of Example 1. Chromatography on silica gel using methanol/chloroform (0-5% methanol, gradient) gave the title compound (0.14g) as a white solid.

50
NMR (δ) (CDCl₃): 0.7-1.05 (8H, m), 1.05-1.4 (11H, m), 1.45 (9H, m), 1.5-1.8 (8H, m), 1.85 (1H, m), 2.55 (2H, m), 2.9-3.2 (2H, m), 4.0-4.65 (8H, m), 5.15 (2H, m), 6.25-6.7 (1H, m), 6.85-7.0 (2H, m), 7.0-7.35 (8H, m).

Example 3

55
Isopropyl 3-(3-(6-(aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate 2TFA.1.5H₂O

This material was formed from isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-

benzoxazin-4-yl)-propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate (Example 2) (0.12g), following the procedure of Description 4(b). This gave the title compound (0.093g) as a white solid.

NMR (δ) (DMSO- d_6): 0.7-1.0 (7H, m), 1.0-1.4 (12H, m), 1.4-1.9 (9H, m), 2.45 (m), 2.75 (1H, m), 2.85-3.1 (1H, m), 3.85-4.1 (3H, m), 4.1-4.4 (1H, m), 4.5-4.7 (3H, m), 4.7-4.85 (0.5H, m), 5.05 (0.5H, m), 6.0 (0.5H, m), 6.35 (0.5H, m), 7.0-7.1 (2H, m), 7.1-7.3 (5.5H, m), 7.35 (0.5H, m), 8.0-8.15 (2H, m), 8.15-8.5 (2H, m).

Analysis: $C_{40}H_{55}N_5O_8 \cdot C_7H_5F_3O_2 \cdot 1.5H_2O$ requires C, 57.7; H, 6.8; N, 8.00%. Found: C, 57.8; H, 6.7; N, 7.7%. M.S. (m/z) (FAB) (M+1) = 734 (consistent with m.w. of free base = 733).

Example 4

Isopropyl 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate.2H₂O

This material was formed from isopropyl 2-(1-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 6(c)) (0.27g) following the procedure of Example 1. Chromatography on silica gel using methanol/chloroform (0-2% methanol gradient) gave the title compound (0.12g) as a white solid.

NMR (δ) (DMSO- d_6): 0.65-1.0 (8H, m), 1.0-1.3 (10H, m), 1.35 (2H, m), 1.4-1.95 (8H, m), 2.45 (2H, m), 2.75 (1H, m), 2.9 (1H, m), 3.1 (0.5N, m), 3.55 (2H, dd), 3.9-4.1 (2H, m), 4.25 (1H, m), 4.35 (1H, m), 4.55 (1H, m), 4.75 (1H, m), 5.0 (0.5H, m), 7.1-7.3 (5H, m), 7.45 (1H, m), 8.05 (0.5H, m), 8.15 (1H, dd), 8.2-8.35 (1.5H, m), 8.35-8.45 (0.5H, m), 8.5 (1H, m).

Analysis: $C_{38}H_{53}N_5O_8 \cdot 2H_2O$ requires C, 60.2; H, 7.3; N, 9.2%. Found: C, 60.1; H, 7.0; N, 9.1%. M.S. (m/z) (FAB) (M+1) = 722 (consistent with m.w. = 721).

Example 5

Isopropyl 3-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate

This material was formed from isopropyl 2-(1-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 7(c)) (0.22g), following the procedure of Example 4.

Analysis: $C_{39}H_{53}N_5O_8 \cdot 2H_2O$ requires C, 60.7; H, 7.4; N, 9.1%. Found: C, 60.7; H, 7.5; N, 9.1%. M.S. (m/z) (FAB) (M+1) = 736 (consistent with m.w. of free base = 735).

Example 6

4-(1-Methylpiperidinyl) 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate

This material was formed from 4-(1-methylpiperidinyl)2-(1-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-2-cyclohexylethyl)-1,3-dithiane-2-carboxylate (Description 8(e)) (0.37g), following the procedure of Example 4.

M.S. (m/z) (FAB) (M+1) = 777 (consistent with m.w. of free base = 776).

Biological Data

In vitro human renin inhibition

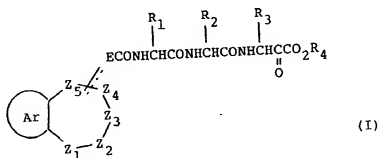
Renin inhibitory activity was estimated as the percentage change in renin activity in human plasma in the presence and absence of compound. The source of plasma was blood taken from healthy volunteers. Renin activity was defined by the difference in angiotensin I levels between two halves of a sample, one incubated at 37° and the other at 4° for 2 h. Angiotensin I levels were measured using a ¹²⁵I- angiotensin I radioimmuno- assay kit (NEN/DuPont, Stevenage). Results were calculated as the mean of at least two duplicate determinations and IC₅₀ values were calculated by linear regression analysis of at least three concentrations of compound.

The results were as follows:

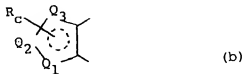
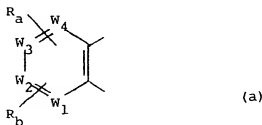
Compound	IC ₅₀ (nm)
E1	15
E3	34
E4	5

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



wherein
the Ar ring is of sub-formula (a) or (b):



one or two of W₁, W₂, W₃ and W₄ is CH, N or NO (such that if two are NO then these are W₁ and W₄), and the others are CH, CR_a or CR_b;

one of Q₁, Q₂ and Q₃ is S and the other two are CH and CR_c;
either Z₁ and Z₂ are absent and Z₃, Z₄ and Z₅ and the carbon atoms to which Z₃ and Z₅ are attached,
form a 5-membered non-aromatic heterocyclic ring; or

Z₁ is absent and Z₂, Z₃, Z₄, Z₅ and the carbon atoms to which Z₂ and Z₅ are attached, form a 6-membered non-aromatic heterocyclic ring; or

Z₁, Z₂, Z₃, Z₄ and Z₅ and the carbon atoms to which Z₁ and Z₅ are attached, form a 7-membered non-aromatic heterocyclic ring;

E is absent or is (CH₂)_n or CH(CH₂)_{n-1} wherein n is 1 to 4;

R_a and R_b are independently selected from hydrogen or a substituent;

R₁ is CH₂R₉ wherein R₉ is optionally substituted aryl or heteroaryl;

R₂ is CHR₁₀R₁₁ wherein R₁₀ is hydrogen or methyl and R₁₁ is C₁₋₆ alkyl, C₃₋₈ cycloalkyl, optionally substituted aryl or heteroaryl, or R₁₁ is amino, C₂₋₇ alkanoylamino, 2-oxopyrrolidinyl, 2-oxopiperidinyl or C₁₋₆ alkoxy-carbonylamino;

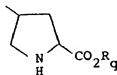
R₃ is CH₂R₁₂ wherein R₁₂ is C₁₋₆ alkyl or C₃₋₈ cycloalkyl or phenyl;

R₄ is C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl-C₁₋₄ alkyl or a group of structure c), d), e) or f);

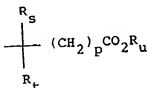
c)



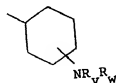
d)



e)



f)



wherein

R_p, R_q, R_s, R_t, R_u and R_w are selected from hydrogen or C₁₋₆ alkyl; or NR_pR_u is 1-imidazolyl; and the dashed line represents an optional bond (when E is present).

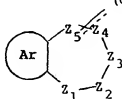
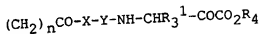
2. A compound according to claim 1 wherein Z₁ and Z₂ are absent, Z₃ is CO, Z₄ is N, Z₅ is CH and E is attached at Z₄.

3. A compound according to claim 1 wherein the Ar ring is of sub-formula (a), W₂ is N and W₁, W₂ and W₄ are CH, CR_a or CR_b, Z₂ is S, Z₃ is CH₂, Z₄ is CO, Z₅ is N and E is attached at Z₅.

4. A compound according to any one of claims 1 to 3 wherein one of R_a and R_b in sub-formula (b) is hydrogen and the other is CH₂NH₂, CO₂H or CH₂NHCH₂CO₂H, or R_c in sub-formula (b) is hydrogen.

5. A compound according to any one of claims 1 to 8 wherein the amino acid residue containing R₂ is Leu, β-pyrrolylalanine or His.

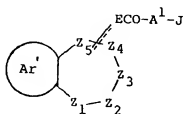
6. A compound according to claim 1 of formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

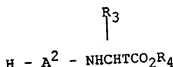
wherein X is Phe;
 Y is Leu or His;
 R₃' is cyclohexylmethyl; and
 the remaining variables are as defined in claim 1.

7. A compound according to any one of claims 1 to 10 wherein E is (CH₂)_n and E is attached at Z₄ or Z₅.
8. A compound according to any one of claims 1 to 11 wherein the carbon atom in R₄ adjacent CO₂, is either a secondary or tertiary carbon atom.
9. A compound according to claim 1, selected from the group consisting of
- isopropyl 3-((2,3-dihydro-1,1-dioxobenzothiophene-3-yl)acetyl-Phe-Leu-amino)-4-cyclohexyl-2-oxobutanoate,
- isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)-amino-4-cyclohexyl-2-oxobutanoate,
- isopropyl 3-(3-(6-(aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxobutanoate,
- isopropyl 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxo-butanoate,
- isopropyl 3-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-4-cyclohexyl-2-oxo-butanoate, and
- 4-(1-methylpiperidiny) 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)-amino-4-cyclohexyl-2-oxobutanoate.
10. A process for the preparation of a compound according to claim 1, which process comprises reacting a reagent of formula (II):



(III)

wherein Ar' is Ar as defined in claim 1, but substituted by R_a', R_b' in sub-formula (a) and by R_c' in sub-formula (b), wherein R_a', R_b' and R_c' are R_a, R_b and R_c respectively or groups or atoms convertible thereto. A¹ is absent or represents an appropriate amino acid or dipeptide unit; J is OH or a leaving group; and the remaining variables are as hereinbefore defined; with a reagent of the formula (IV):



(IV)

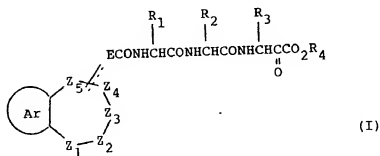
wherein

A^1 is absent or represents an appropriate amino acid or dipeptide unit, such that $A^1 + A^2$ is $-NHCH(R_1)CONHCH(R_2)CO-$; T is an optionally protected carbonyl group; and the remaining variables are $-NHCH(R_1)CONHCH(R_2)CO-$; and thereafter, if desired or necessary deprotecting (T or within A^1 or A^2) of as hereinbefore defined; and/or converting Z_1, Z_2, Z_3, Z_4 or Z_5 to other Z_1, Z_2, Z_3, Z_4 or $Z_5, R_3/R_4/R_5$ in A^1 to the products, and/or converting Z_1, Z_2, Z_3, Z_4 or Z_5 to other Z_1, Z_2, Z_3, Z_4 or $Z_5, R_3/R_4/R_5$ in A^1 to the products, and/or forming a pharmaceutically acceptable salt thereof.

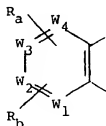
11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9, and a pharmaceutically acceptable carrier.
12. A compound according to any one of claims 1 to 9 for use as an active therapeutic substance.
13. A compound according to any one of claims 1 to 9 for use in the treatment of hypertension.
14. Use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of hypertension.

Claims for the following Contracting State: ES

1. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof:



wherein
the Ar ring is of sub-formula (a) or (b):



(a)



(b)

one or two of W_1 , W_2 , W_3 and W_4 is CH , N or NO (such that if two are NO then these are W_1 and W_4), and the others are CH , CR_a or CR_b ;

one of Q_1 , Q_2 and Q_3 is S and the other two are CH and CR_c ;

either Z_1 and Z_2 are absent and Z_3 , Z_4 and Z_5 and the carbon atoms to which Z_3 and Z_5 are attached, form a 5-membered non-aromatic heterocyclic ring; or

Z_1 is absent and Z_2 , Z_3 , Z_4 , Z_5 and the carbon atoms to which Z_2 and Z_5 are attached, form a 6-membered non-aromatic heterocyclic ring; or

Z_1 , Z_2 , Z_3 , Z_4 and Z_5 and the carbon atoms to which Z_1 and Z_5 are attached, form a 7-membered non-aromatic heterocyclic ring;

E is absent or is $(CH_2)_n$ or $CH(CH_2)_{n-1}$ wherein n is 1 to 4;

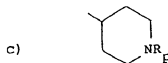
R_a and R_b are independently selected from hydrogen or a substituent;

R_1 is CH_2R_9 wherein R_9 is optionally substituted aryl or heteroaryl;

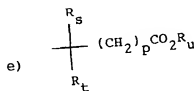
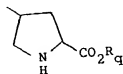
R_2 is $CHR_{10}R_{11}$ wherein R_{10} is hydrogen or methyl and R_{11} is C_{1-6} alkyl, C_{3-8} cycloalkyl, optionally substituted aryl or heteroaryl, or R_{11} is amino, C_{2-7} alkanoylamino, 2-oxopyrrolidinyl, 2-oxopiperidinyl or C_{1-6} alkoxy-carbonylamino;

R_3 is CH_2R_{12} wherein R_{12} is C_{1-6} alkyl or C_{3-8} cycloalkyl or phenyl;

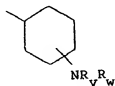
R_4 is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl- C_{1-4} alkyl or a group of structure c), d), e) or f):



d)



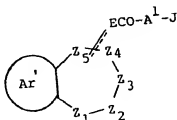
f)



wherein

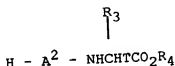
R_p , R_q , R_s , R_t , R_u , R_v and R_w are selected from hydrogen or C_{1-6} alkyl; or NR_vR_w is 1-imidazolyl; and

the dashed line represents an optional bond (when E is present);
which process comprises reacting a reagent of formula (III):



(III)

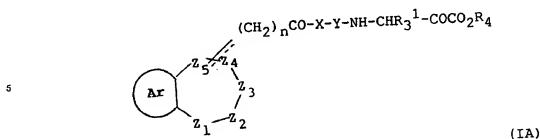
wherein Ar' is Ar as defined in claim 1, but substituted by R_a', R_b' in sub-formula (a) and by R_c' in sub-formula (b), wherein R_a', R_b' and R_c' are R_a, R_b and R_c respectively or groups or atoms convertible thereto. A' is absent or represents an appropriate amino acid or dipeptide unit; J is OH or a leaving group; and the remaining variables are as hereinbefore defined; with a reagent of the formula (IV):



(IV)

wherein
A² is absent or represents an appropriate amino acid or dipeptide unit, such that A¹ + A² is -NHCHR₁CONHCHR₂CO-; T is an optionally protected carbonyl group; and the remaining variables are as hereinbefore defined; and thereafter, if desired or necessary deprotecting (T or within A¹ or A²) of the products, and/or converting Z₁, Z₂, Z₃, Z₄ or Z₅ to other Z₁, Z₂, Z₃, Z₄ or Z₅; R_a'/R_b'/R_c' in Ar' to R_a, R_b, and/or R_c and/or W₁, W₂, W₃ or W₄ in Ar' when N to NO; and/or forming a pharmaceutically acceptable salt thereof.

2. A process according to claim 1 wherein Z₁ and Z₂ are absent, Z₃ is CO, Z₄ is N, Z₅ is CH and E is attached at Z₄.
3. A process according to claim 1 wherein the Ar ring is of sub-formula (a), W₃ is N and W₁, W₂ and W₄ are CH, CR₃ or CR₃, Z₂ is S, Z₃ is CH₂, Z₄ is CO, Z₅ is N and E is attached at Z₅.
4. A process according to any one of claims 1 to 3 wherein one of R_a and R_b in sub-formula (b) is hydrogen and the other is CH₂NH₂, CO₂H or CH₂NHCH₂CO₂H, or R_c in sub-formula (b) is hydrogen.
5. A process according to any one of claims 1 to 8 wherein the amino acid residue containing R₂ is Leu, β-pyrazolylalanine or His.
6. A process according to claim 1 for the preparation of a compound of formula (IA) or a pharmaceutically acceptable salt thereof.



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wherein
 X is Phe;
 Y is Leu or His;
 R₃¹ is cyclohexylmethyl; and
 the remaining variables are as defined in claim 1.

7. A process according to any one of claims 1 to 10 wherein E is (CH₂)_n and E is attached at Z₄ or Z₅.
8. A process according to any one of claims 1 to 11 wherein the carbon atom in R₄ adjacent CO₂ is either a secondary or tertiary carbon atom.
9. A process according to claim 1, for the preparation of a compound selected from the group consisting of
- isopropyl 3-((2,3-dihydro-1,1-dioxobenzothiophene-3-yl)acetyl-Phe-Leu-amino)-4-cyclohexyl-2-oxo-
 butanoate,
- isopropyl 3-(3-(6-(BOC-aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)-
 amino-4-cyclohexyl-2-oxobutanoate,
- isopropyl 3-(3-(6-(aminomethyl)-2,3-dihydro-3-oxo-4H-1,4-benzoxazin-4-yl)propanoyl-Phe-Leu)amino-4-
 cyclohexyl-2-oxobutanoate,
- isopropyl 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)amino-4-
 cyclohexyl-2-oxo-butanoate,
- isopropyl 3-(4-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)butanoyl-Phe-Leu)amino-4-
 cyclohexyl-2-oxo-butanoate, and
- 4-(1-methylpiperidinyl) 3-(3-(2,3-dihydro-3-oxo-4H-pyrido[4,3-b]-1,4-thiazin-4-yl)propanoyl-Phe-Leu)-
 amino-4-cyclohexyl-2-oxobutanoate.
10. Use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of hypertension.

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EUROPEAN SEARCH REPORT

Application Number

EP 90 31 3104

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 296 581 (SQUIBB & SONS INC.) * Claims 1,10,11 * -----	1-10	C 07 K 5/02 C 07 K 5/06 A 61 K 37/64
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 K A 61 K
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of search 14 March 91	Examiner DEFFNER C-A.E.
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention		E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons S: member of the same patent family, corresponding document	